Issues of Polymorphism and Abbreviated New Drug Applications

21CFR 314.92 (a)(1) addresses drug products which may be suitable for filing as an abbreviated new drug application (ANDA), and reads in part " Drug products that are the same as a listed drug….For determining the suitability of an abbreviated new drug application, the term "same as" means identical in active ingredients(s), dosage form, strength, route of administration, and conditions of use…"

The existence of different physical forms of a drug substance has provided a basis for arguments concerning drug substance identity and suitability for use in drug products approved under 505(j) of the Federal Food, Drug, and Cosmetic Act. The arguments, for the most part, relate to the requirements for "sameness" that such products must meet. Additional issues relate to the characteristics of drug products that are manufactured using different physical forms of a drug substance.

Monographs that appear in the United States Pharmacopeia (USP) are relevant to FDA's consideration of an ANDA drug product. Such monographs are one source of specifications for each drug substance and drug product on such matters as identification, dissolution, and assay. Because by regulation, USP is recognized as an official compendium, the monograph drug substance and drug product nomenclature may serve as the "official" or "established name". Restrictions on physical form, either in the monograph description or by specific test (such as crystallinity) can affect the use of the established name.

For drug substances or drug products that are not subject to USP monographs, there may still be constraints on the use of other forms of the drug substance, such as product labeling or patents. In such cases, identity or sameness arguments might be based on differences in physical characteristics of the drug substance forms, leading to potential differences in drug product performance.

A variety of legal and scientific positions, based on these and other topics, have been raised as arguments that certain ANDAs can not be shown to meet "sameness " requirements and therefore are not approvable. Alternative arguments propose that specific testing requirements be imposed as conditions of approval.

Although the attached citizen petition response is directed at only one product, the discussion addresses several different topics and is instructive of the various legal and scientific issues raised.

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Agency Position on Polymorphism and Abbreviated New Drug Applications

For a generic drug product to be regarded as having the same active ingredient under section 314.92(a)(1), the drug substance in a proposed generic drug product need not have the same physical form as the drug substance in the reference listed drug. FDA states in its *Approved Drug Products With Therapeutic Equivalence Evaluations* (*Orange Book*) that the Agency considers drug products containing different polymorphs of the same drug substance to be pharmaceutically equivalent. The *Orange Book* describes pharmaceutical equivalents as, among other things, containing the same active ingredient(s). Therefore, FDA regards different polymorphs of a drug substance as the same active ingredient.

Also, the *Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances*, issued February 1987, in discussion of the relationship of solid-state drug substance forms to bioavailability, notes the following:

> Some drug substances exist in several different crystalline forms ("polymorphs"), due to a different arrangement of molecules in the crystal lattice, which thus show distinct differences in their physical properties. The same drug substance may also exist in a noncrystalline (amorphous) form. These various forms differ in their thermodynamic energy content, *but not in composition*.

As the Guideline points out, the polymorphic form of a drug substance can affect the dissolution and bioavailability of drug products. Thus, it is possible that a difference in physical form of the active ingredients might prevent a proposed generic drug from being bioequivalent to the reference listed drug (thus barring approval of the ANDA). However, this difference in bioequivalence would not mean that the generic and reference listed drug products contained different active ingredients; it would mean that the *drug products* would *not* be the "same." If however, the drug product had been shown to be bioequivalent to the reference listed drug, in addition to meeting other requirements, the drug product would be considered to be the same, and could be approved.

Reprints from the Orange Book, USP, and CDER Drug Substance Guideline providing additional information are attached.

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